REMARKS

The present application is directed to compositions containing a biologically active agent and a polycationic carbohydrate, wherein the biologically active agent is capable of generating a protective immune response in an animal. Claims 1, 3, 5-6, 11-17, 20-22, 37, 40-43 are pending. Claims 2, 4, 7-10, 18-19, 23-36 and 38-39 are cancelled. Claims 41-43 are new. Support for the amendments is found throughout the specification, and no new matter is introduced. In light of the following remarks, favorable consideration of the present application is respectfully requested.

Claim objections

In the Final Office Action mailed June 28, 2007, the Examiner objected to Claim 37 under 37 C.F.R. 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully submit that Claim 37 is amended herein to specify certain biologically active agents. Support for this amendment can be found at least on page 5, lines 14-20 of the present application. Accordingly, applicants respectfully request withdrawal of the objection under 37 C.F.R. 1.75(c).

Claim rejections under 35 U.S.C. §103(a)

In the Final Office Action mailed June 28, 2007, the Examiner rejected Claims 1, 3, 6, 11-17, 37 and 40 under 35 U.S.C. §103(a), as being unpatentable over Eyles *et al.* (*Vaccine*, 1998) (hereinafter "Eyles") in view of Kotze *et al.* (*International J. of Pharm.*, 1997) (hereinafter "Kotze"). Applicants respectfully submit that the amendments to the claims overcome the rejection.

Eyles fails to teach or suggest a composition containing a **polycationic carbohydrate** and, because Eyles is silent with respect to polycationic carbohydrates, the Eyles reference fails to teach a polycationic carbohydrate possessing an increased degree of **quaternization**. Eyles is directed to method of stabilizing vaccine antigens. This goal is achieved through microencapsulation of *Yersinia pestis* sub-units (F1 and V antigens). As explained by Eyles, the antigens are microencapsulated because "simple mucosal application of antigenic proteins, for example in the gastrointestinal or respiratory tracts, is usually **ineffective**

in terms of vaccination. Enzymatic or chemical destruction, combined with poor absorption into sub-epithelia compartments dictate that mucosally administered vaccines usually require some form of adjuvant or delivery vehicle." (see page 699, left hand column). Eyles goes on to characterize the effects of microencapsulation and reports increased efficacy when the antigens are microencapsulated. At no point does Eyles discuss the need for or use of a polycationic carbohydrate.

Applicants direct the Examiner to Example 3 of the present application where compositions (not microencapsulated) comprising F1 and V antigens and at least 20% quaternization trimethyl chitosan **augmented** the humoral response to F1 and V antigens via intranasal administration. Based on the teachings of Eyles, and the state of the art at that time, one of ordinary skill in the art would have found applicants' result to be result **surprising and unexpected** because Eyles had demonstrated that such antigens must be **microencapsulated** to be effective. It is to the applicants' credit that they have developed a composition comprising a biologically active agent and a polycationic carbohydrate such that the biologically active agent can be effective even when the composition is not microencapsulated as described in Example 3.

The deficiencies of Eyles are not satisfied by Kotze for at least the following reasons. Kotze discloses that normal **chitosan** salts are **ineffective** as absorption enhancers (See Abstract). Specifically, Kotze teaches that a composition comprising chitosan is **undesirable** because "at neutral and basic pH values, the chitosan molecules will lose their charge and therefore the potential use of this polymer, especially in more neutral or basic environments such as those found in the large intestine and colon, is limited" (see page 253, right hand column). Applicants respectfully submit that one of ordinary skill in the art, based on the teachings of Kotze, would **not** be motivated to combine a biologically active agent with **chitosan**.

In contrast to Kotze's adverse view of chitosan molecules, applicants unexpectedly found that a composition **containing** chitosan was **more** immunologically effective than a composition **lacking** chitosan. (see Example 2 of the instant application).

Kotze discloses the use of two quaternized trimethyl chitosans (12.3% and 61.2%, quaternization respectively) in conjunction with hydrophilic compounds. However, as disclosed by Kotze, trimethyl chitosan with 12.3% quaternization was **ineffective** at neutral pH. Therefore, applicants submit that one of ordinary skill in the art reading the Kotze reference would **avoid** a

composition containing trimethyl chitosan with at least **20%** quaternization as claimed in amended Claim 1.

Applicants submit that the teachings of Kotze are **not transferable** and would fail to teach a reasonable expectation of success as suggested by the Examiner. First, Kotze uses **hydrophilic** compounds in combination with a **solution** of trimethyl chitosan. In contrast, the instant application discloses a composition comprising a biologically active agent that allows for the delivery of **hydrophobic** compounds, such as the F1 antigen of *Yersinia pestis*, that would not normally dissolve or be soluble in an aqueous medium (see page 6, lines 22-26 and Example 3). Second, applicants have amended Claim 1 to clarify that the composition is for administration to **mucosal** surfaces. Support for this amendment can be found on page 8, lines 25-26 of the present application. Applicants submit that the testing performed by Kotze is directed to **intestinal cells** and is not a suitable model applicable for a composition adapted for administration to mucosal cells.

For at least the foregoing reasons, applicants respectfully submit that the methodology of Kotze is not directly applicable to the teachings of Eyles, and thus the result of Kotze cannot be readily applied to the teachings of Eyles.

Applicants submit that, even if one of ordinary skill in the art were to combine Kotze and Eyles, which applicants do not concede, it would **not** lead the skilled person to arrive at the claimed composition because Eyles teach that biologically active agents (F1 and V antigens of *Y. pestis*) are stabilized by **microencapsulation**. In addition, Kotze teaches that chitosan and quaternization trimethyl chitosan are not effective at pH 7.4. Clearly the disclosures address different technical problems and, as such, there would be no motivation for one of ordinary skill in the art to combine the teachings without the benefit of hindsight. As stated above, neither Eyles or Kotze teach or suggest the claimed composition.

Claims 3, 6, 11-17, 37 and 40 depend directly or indirectly on Claim 1. Accordingly, applicants submit that Claims 1, 3, 6, 11-17, 37 and 40 are non-obvious in view of the cited references. As discussed above, applicants respectfully submit that the claimed compositions are non-obvious. Accordingly, applicants submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Final Office Action mailed June 28, 2007, the Examiner rejected Claims 1, 3, 6, 11-12, 16, 37 and 40 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576)(hereinafter "Illum") in view of Kotze. Applicants respectfully traverse.

Illum discloses the use of **chitosan glutamate** as an adjuvant in an intranasal vaccine. Combining the teachings of Illum with Kotze might simply motivate one of ordinary skill in the art to substitute trimethyl chitosan for chitosan glutamate and, for the reasons set out above, would **teach away** from using trimethyl chitosans with a degree of quaternization that is at least 20%.

Furthermore, the deficiencies of Illum are not satisfied by Kotze for at least the following reasons. As explained above, Kotze fails to teach or suggest a composition comprising a biologically active agent that is capable of generating a **protective immune response** in an animal and a polycationic carbohydrate possessing at least 20% quaternization.

Applicants submit that, based on the teachings of Kotze, one skilled in the art would lack the motivation to derive a composition comprising a polycationic carbohydrate of at least 20% quaternization because Kotze reports that a trimethyl chitosan with 12.3% quaternization is **ineffective** at neutral and acidic pH (see page 255, second paragraph).

Furthermore, Kotze discloses that normal **chitosan** salts are ineffective as absorption enhancers (See Abstract). Specifically, Kotze teaches that a composition comprising chitosan is **undesirable** because "at neutral and basic pH values, the chitosan molecules will lose their charge and therefore the potential use of this polymer, especially in more neutral or basic environments such as those found in the large intestine and colon, is limited" (see page 253, right hand column). Therefore, applicants respectfully submit that one of ordinary skill in the art based on the teachings of Kotze would avoid combining a biologically active agent with a polycationic carbohydrate having at least 20% quaternization, as claimed herein.

Moreover, applicants respectfully submit Kotze fails to teach a biologically active agent capable of generating a protective immune response. Kotze discloses **hydrophilic** compounds such as mannitol and polyethylene glycol.

Claims 3, 6, 11-12, 16, 37 and 40 depend directly or indirectly from Claim 1. As discussed above, applicants respectfully submit that the compositions of the instant application are non-obvious over the teachings of Illum and Kotze.

Accordingly, applicants respectfully submit that Illum and Kotze fail to provide a case of *prima facie* obviousness because neither Illum nor Kotze teach or suggest the compositions as claimed. For at least the foregoing reasons, applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Final Office Action mailed June 28, 2007, the Examiner rejected Claims 1, 3, 5-6, 11-12, 20-22 37 and 40 under 35 U.S.C. §103(a), as being unpatentable over Duncan *et al.,* (WO 94/20070) (hereinafter "Duncan") in view of Kotze. Applicants respectfully traverse.

Duncan teaches that antigens are more effective when combined with adjuvants and mucoadhesives. Duncan, therefore teaches compositions that produce enhanced immune responses.

Kotze **teaches away** from using chitosans in general, and specifically discloses that a trimethyl chitosan with 12% degree of quarternization was **ineffective** at physiological pH (pH 7.4).

Accordingly, applicants respectfully submit that Kotze and Duncan fail to make the claimed composition *prima facie* obvious because neither Kotze nor Duncan, alone or in combination, teach or suggest the compositions as claimed.

Claims 3, 5-6, 11-12, 20-22, 37 and 40 depend directly or indirectly from amended Claim 1 and contain all the limitations thereof. As discussed above, applicants respectfully submit that the compositions of the instant application are non-obvious over the teachings of Duncan and Kotze. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection under 35 U.S.C. §103(a).

CONCLUSION

Based upon the amendments and remarks provided above, applicants believe that the pending claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6500 is respectfully solicited.

Respectfully submitted,

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